Convegno Regionale Aiom
EMILIA ROMAGNA

I NUMERI DEL CANCRO IN EMILIA ROMAGNA:
AMBIENTE, STILI DI VITA, SCREENING
FOCUS SU TUMORI DEL POLMONE E COLON-RETTO

Centro Servizi Università Policlinico di Modena
Modena, 23 novembre 2018

Presidente dell'evento:
Gabriele Luppi

Tumori del colon retto
Nuovi standard 2018?

Giordano D. Beretta
Presidente eletto AIOM
Oncologia Medica
Humanitas Gavazzeni Bergamo

Conflitto d'interessi

Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- **Partecipazione ad Advisory Board:**
  - **Roche**
  - **Lilly**
  - **Servier**
- **Spese per invito a convegni**
  - **Roche**
  - **Servier**
  - **Celgene**
  - **Ipsen**
  - **Sanofi**

What have we learnt so far?

	Right-sided	Left-sided
Clinical differences[1]	More common in women	More common in men
	MUTYH-associated polyposis	Familial adenomatous polyposis
Molecular differences[1,2]	PIK3CA mutation	HER2 overexpression
	BRAF mutation	KRAS mutation
	dMMR/MSI-H	High AREG-EREG expression
	CIMP-high	TP53 mutation
	Low AREG-EREG expressions	APC
	CMS1 (immune)	CMS2 (canonical)
Prognostic impact[1]	Poorer prognosis	Better prognosis

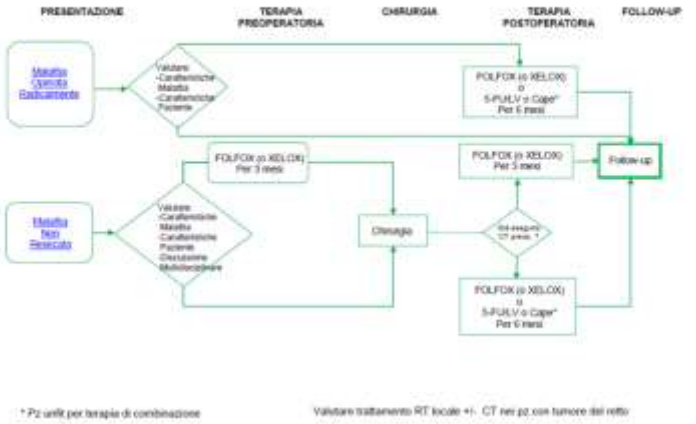
1. Lee GH, et al. Eur J Surg Oncol 2015;41:300–308; 2. Stintzing S, et al. E J Cancer 2017;84:69–80; 3. Tejpar S, et al. JAMA Oncol 2017;3(2):194–201; 4. Venook AP, et al. ASCO 2016 (Abstract No. 3504).

Cosa non è cambiato dal 2017

Diagnosi e stadiazione

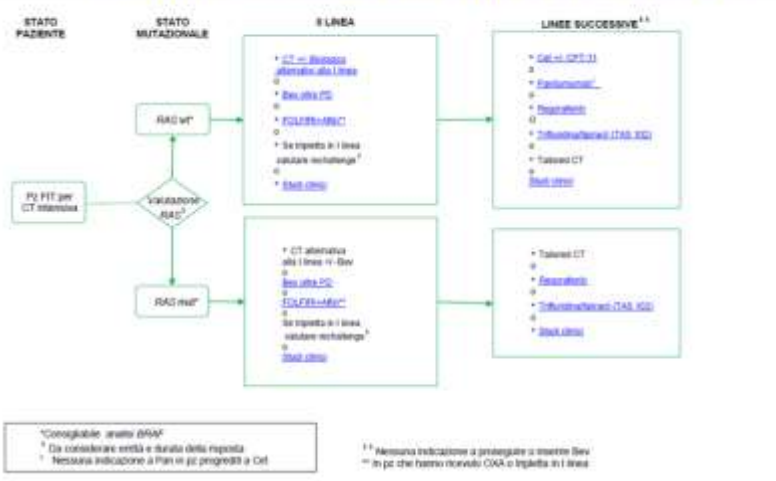
Figura 1: Diagnosi e Stadiazione

Malattia metastatica resecabile

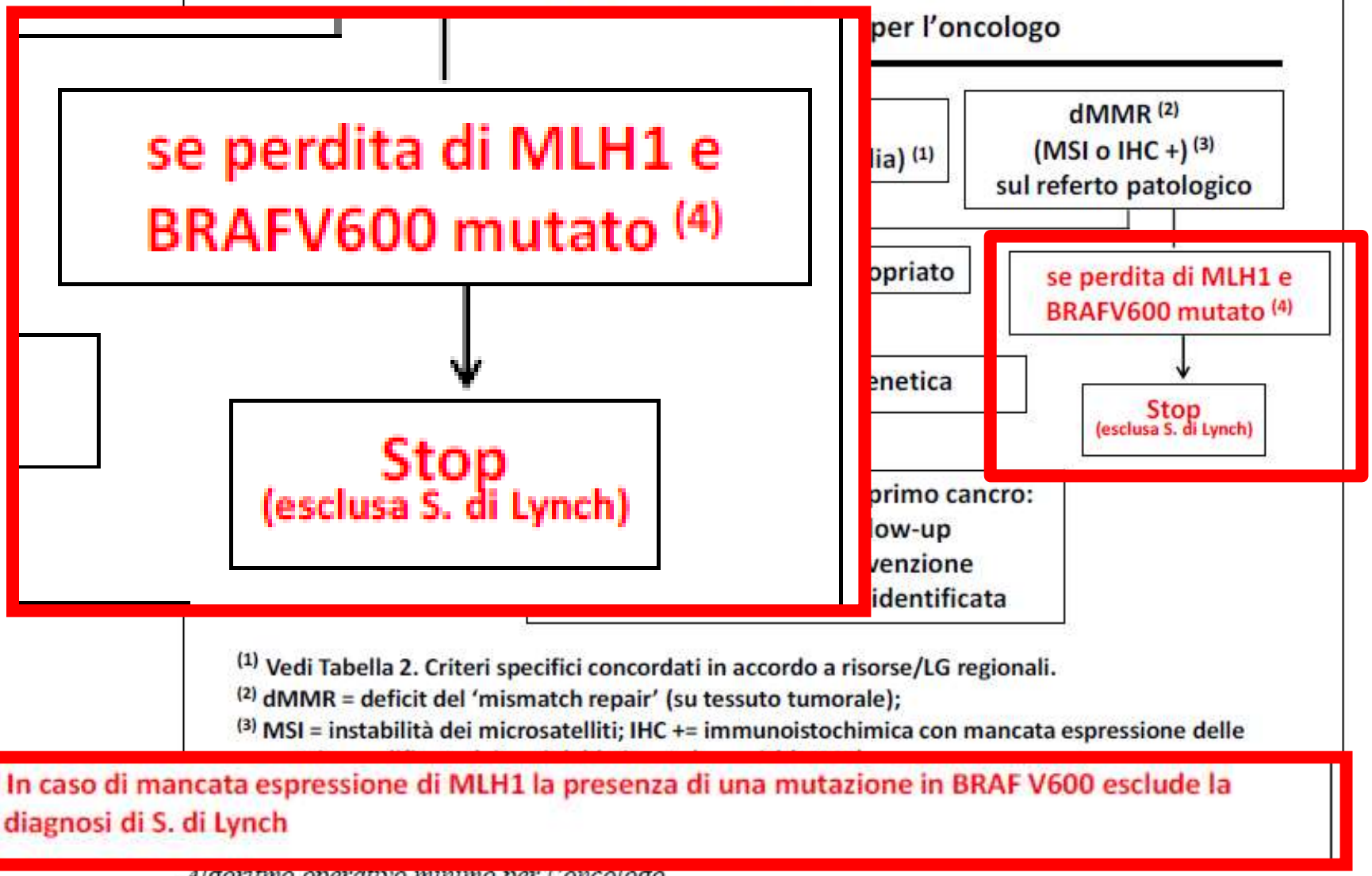


Malattia metastatica

Malattia metastatica linee successive



Sindromi genetiche



Algoritmo operativo minimo per l'oncologo

Il Mantenimento

LG AIOM 2015 – 2016–2017

QUESITO 3: Nei pazienti con tumore del colon-retto metastatico dopo un t… chemioterapia e bevacizumab è indicato proseguire con una terapia di mantenimento … chemioterapia?

RACCOMANDAZIONE:

Nei pazienti con tumore del colon-retto metas… …ia e bevacizumab può essere considerato prosegui… **Bevacizumab +/- fluoropirimidine** fluoropirimidina, da valutare caso per caso, sia sulla base del beneficio atteso, del rischi e della motivazione del paziente.

Forza della raccomandazione: POSITIVA DEBOLE

Motivazioni/Commenti al bilancio Beneficio/Danno: sulla base dei dati disponibili (nessun vantaggio in OS, costi, safety, disegno degli studi) il panel non ha potuto definire una posizione certa, che fosse a favore o contraria, in merito al bilancio beneficio/danno.

Votazione forza raccomandazione				Votazione bilancio Beneficio/Danno		
Positiva forte	Positiva debole	Negativa debole	Negativa forte	Favorevole	Incerto	Sfavorevole
0	5	3	0	1	6	1

Qualità globale delle evidenze: MODERATA

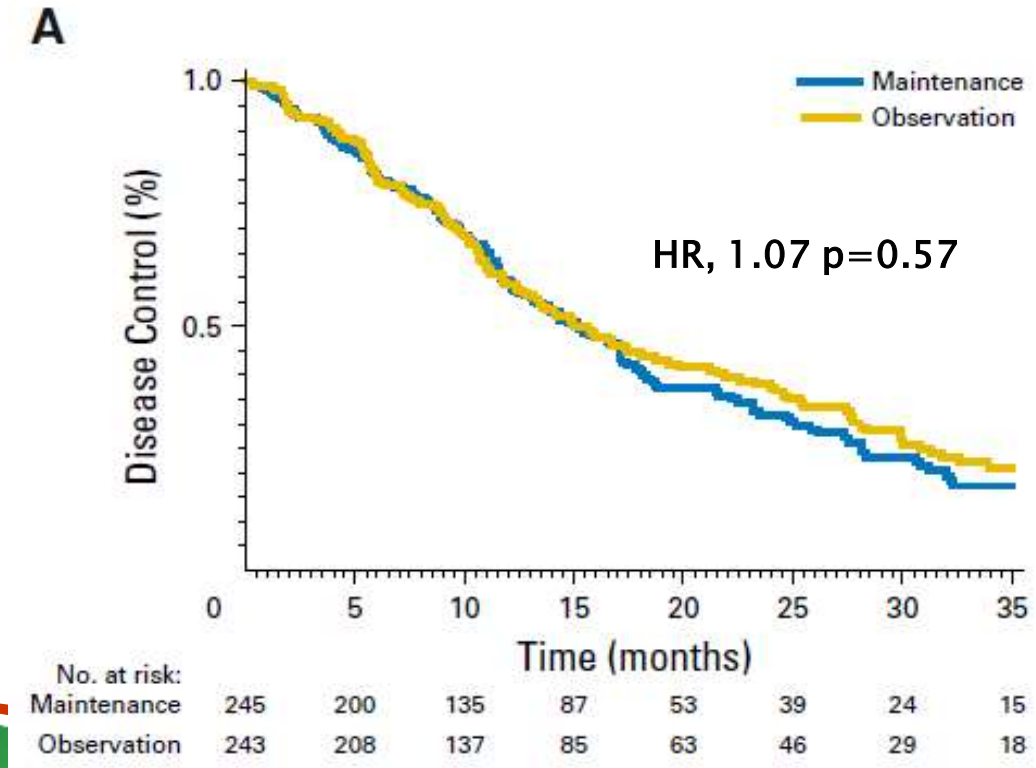
Il Mantenimento

VOLUME 36 · NUMBER 7 · MARCH 1, 2018

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Bevacizumab Maintenance Versus No Maintenance During Chemotherapy-Free Intervals in Metastatic Colorectal Cancer: A Randomized Phase III Trial (PRODIGE 9)

Thomas Aparicio, Francois Ghiringhelli, Valérie Boige, Karine Le Malicot, Julien Taieb, Olivier Bouché, Jean-Marc Phelip, Eric François, Christian Borel, Roger Faroux, Laetitia Dahan, Stéphane Jacquot, Dominique Genet, Faiza Khemissa, Etienne Suc, Françoise Desseigne, Patrick Texereau, Come Lepage, Jaafar Bennouna, and PRODIGE 9 Investigators



Oncologia Medica HUMANITAS GAVAZZENI

Il Mantenimento

LG AIOM 2018

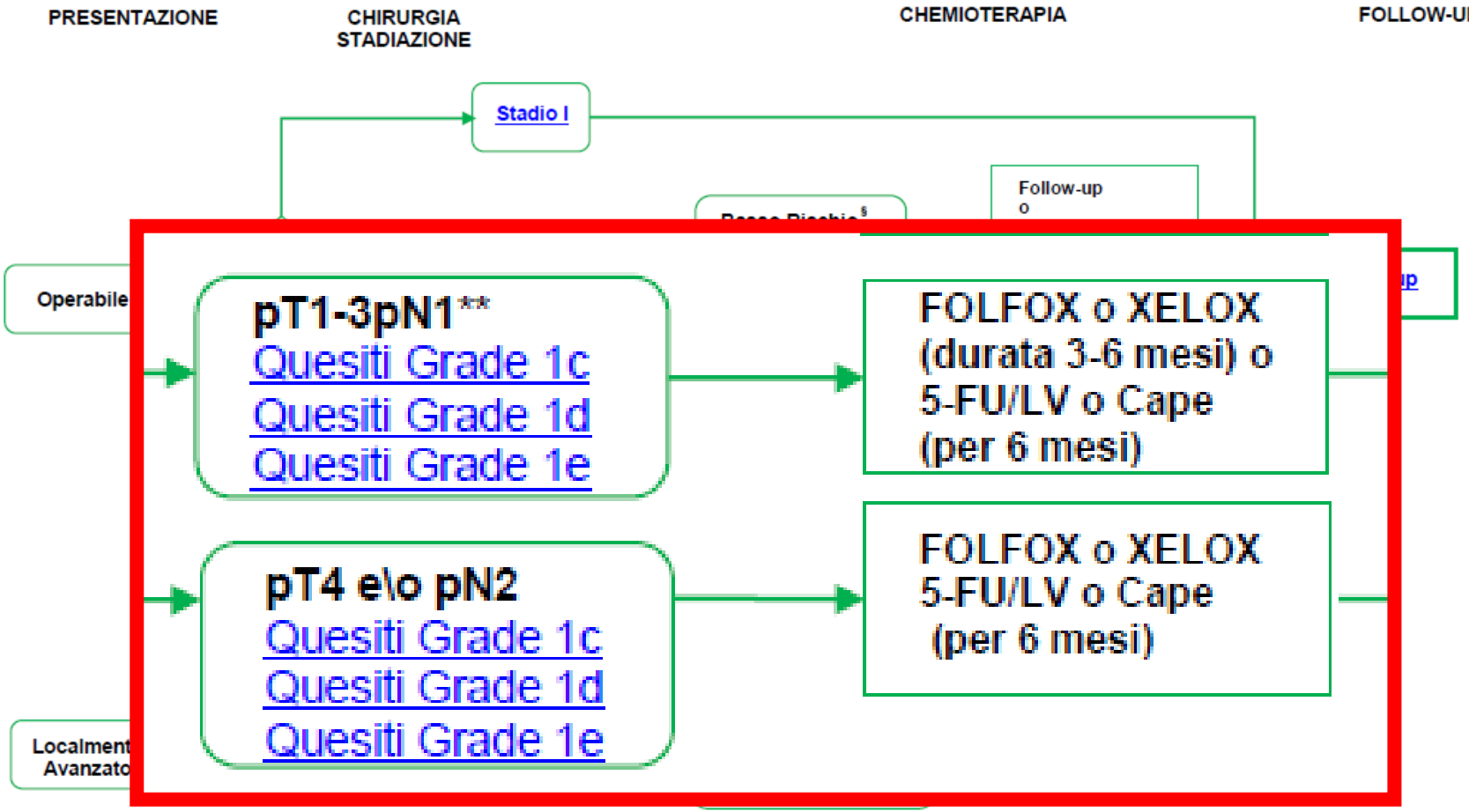
Qualità dell'evidenza GRADE	Raccomandazione	Forza della raccomandazione clinica
Moderata	Nei … un tratt… mab può … di man… da valutare caso per caso, sia sulla base del beneficio atteso, dei rischi e della motivazione del paziente (9, 10).	Positiva debole

Bevacizumab + fluoropirimidine puo'essere considerato

Qualità dell'evidenza GRADE	Raccomandazione	Forza della raccomandazione clinica
Bassa	Nei p… o un tratta… mab, una … non dovre… rima intenzione (8).	Negativa debole

Solo bevacizumab non dovrebbe essere considerato

Colon: Malattia non metastatica



*Sconsigliato bevacizumab se protesi
**Senza altri fattori di rischio.
§ Basso rischio: consigliabile valutazione instabilità dei microsatelliti
§§ Alto rischio: ≥1 fattore di rischio (T4, G3-G4, <12 lfn asportati, esordio con occlusione/perforazione, invasione vascolare, linfatica o perineurale)
Adottare particolare cautela nei pazienti over 70-75aa, dove l'aggiunta dell'oxaliplatino mostra un beneficio ridotto.

Adiuvante
3 vs 6

LG AIOM 2017

al momento

Nel complesso [illegible] la pratica clinica [illegible] lo standard 6 mesi [illegible] ragionevole prendere in considerazione una durata del trattam[illegible] 3 mesi (tre mesi) nel caso di insorgenza di tossicita' (neurotossicita') durante la terapia. In pazienti radicalmente operati per adenocarcinoma del colon pT3, pN[illegible] pT3, pN1 senza ulteriori fattori di rischio [illegible] fluoropirimidina è somministrata per via orale.

fluoropirimidina orale

NO Pubblicazione
NO Raccomandazione

(Pre)history of adjuvant therapy

- 1990: 5-FU/lev superior to surgery alone
- 1994: 5-FU/LV superior to surgery alone
- 1998: 5-FU/LV superior to 5-FU/lev; 6- and 12-month treatment cycles equivalent; Lev unnecessary; High-dose and low-dose LV equivalent; Monthly and weekly treatment equivalent
- 2002: LV5FU2 and monthly bolus equivalent

Fluoropyrimidines and oxaliplatin

(X-ACT, MOSAIC, NSABP C07, XELOXA)

Benefit in stage III patients:

- Fluoropyrimidines risk of death reduction: 10-15%
- OXA addition to risk of death reduction: 4-6%
- Both FOLFOX and XELOX (CAPOX) acceptable
- Neurological toxicity is an issue

Evolution of duration

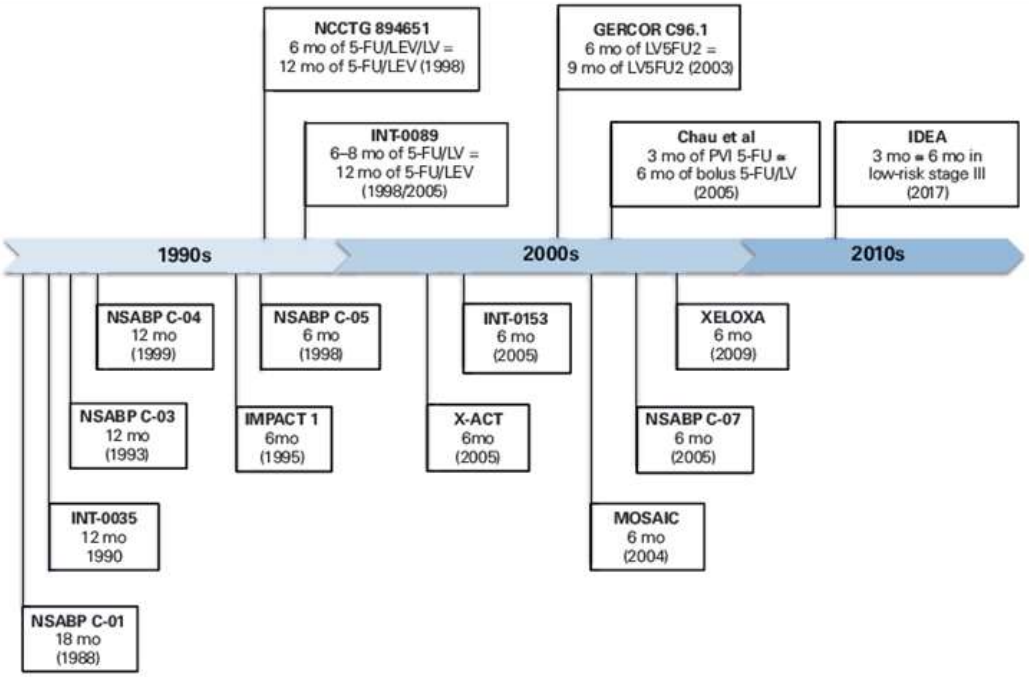
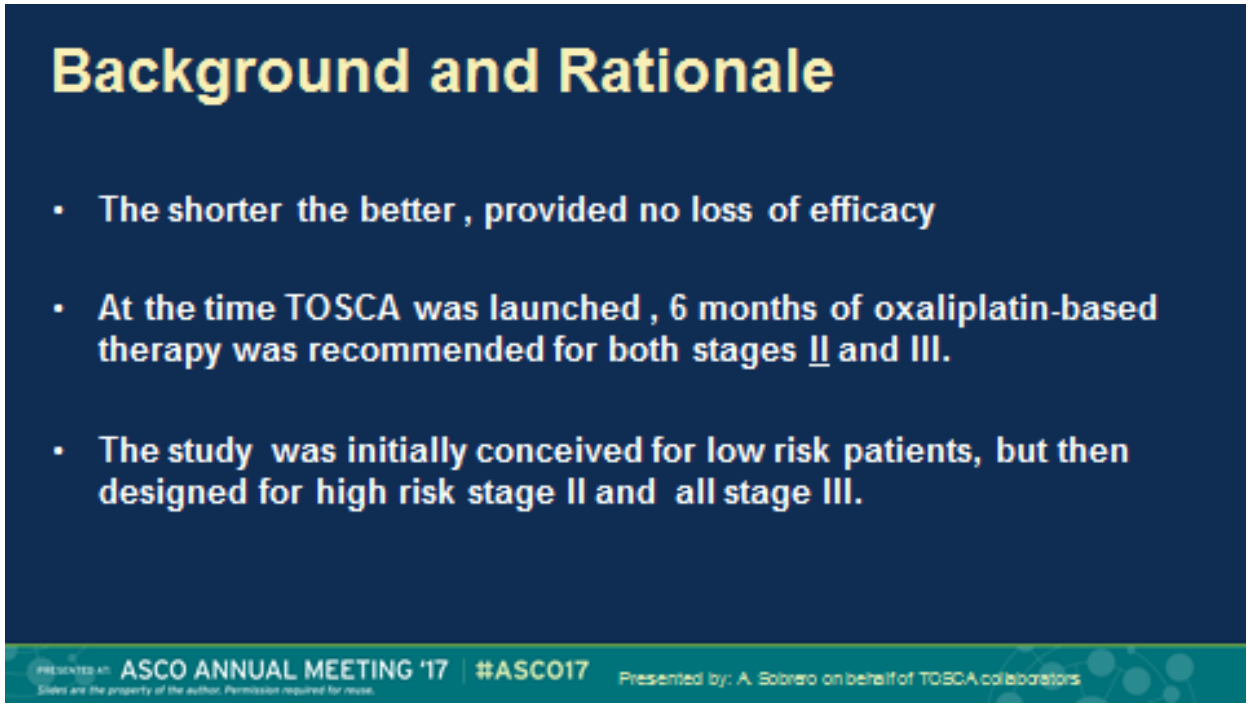


Figure. The Evolution of the Duration of Adjuvant Chemotherapy.
5-FU = fluorouracil; IDEA = International Duration Evaluation of Adjuvant; LEV = levamisole; LV = leucovorin; LV5FU2 = infusional 5-FU/LV; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; PVI = protracted venous infusion; X-ACT = Xeloda in Adjuvant Colon Cancer Therapy.

MUNICH 2018 ESMO congress

R. Labianca Educational

Italian idea made in Sobrero



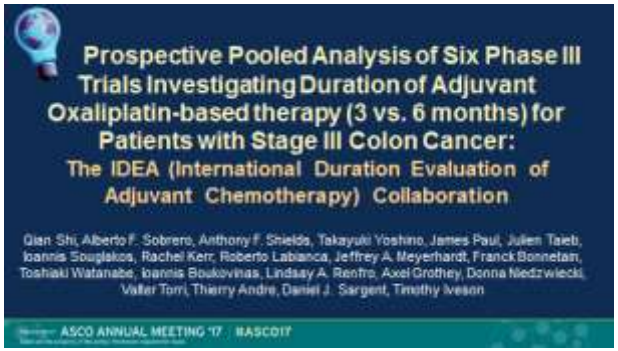
- **Three**
- **Or**
- **Six**
- **Colon**
- **Adjuvant trial**

- **Stadi II ad alto rischio**
- **Stadi III**
- **Seconda randomizzazione nei III ad alto rischio +/- Bevacizumab**

Shortening adjuvant treatment in Colorectal Cancer

International Duration Evaluation of Adjuvant chemotherapy

- **Francesi ed inglesi sviluppano (IDEA loro o me-too?) la stessa ipotesi**
- **→nasce il proposito di una pooled analysis pre-pianificata di più studi con lo stesso quesito**
  - **→Vantaggio: ottenere un campione di maggiori dimensioni con una maggiore potenza statistica**



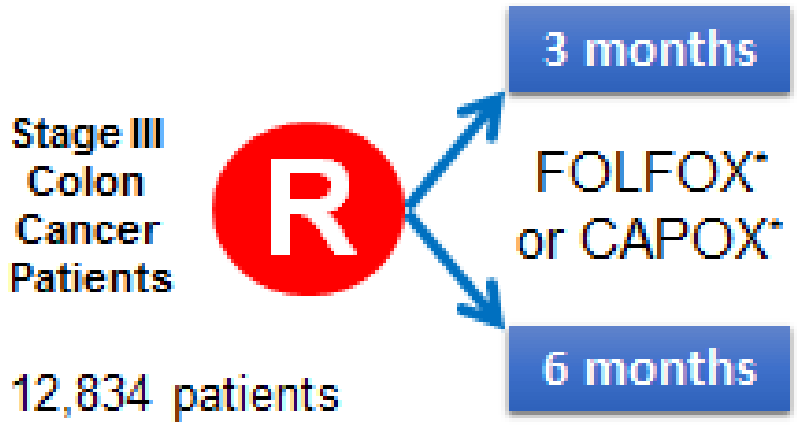
IDEA

Shortening adjuvant treatment in Colorectal Cancer

- **Fluoropirimidina + oxaliplatino per 6 mesi è lo standard di trattamento della terapia adiuvante nel III stadio dal 2004**
- **Fattore limitante di tale associazione è la neurotossicità**
- **Può un trattamento di minore durata essere altrettanto efficace riducendo la tossicità?**

➢ **12.834 pazienti randomizzati**

Study Overview



*Investigator's choice, no randomization

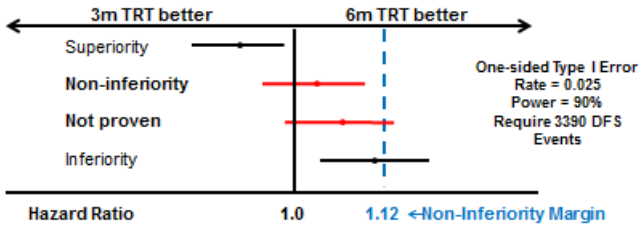
Primary endpoint: DFS

IDEA

- **Objective:**
  Reduce side-effects of therapy without giving up (too much) anti-cancer efficacy of therapy
- **Non-inferiority design:**
  As agreed upon by patient advocates and oncologists, shorter duration of therapy should not sacrifice more than 12% of benefit of adjuvant therapy
  In statistical terms: upper 95% confidence interval of Hazard Ratio (HR) of disease free survival (DFS) should not exceed ***1.12***

Non-inferiority Hypothesis Testing

Statistical Conclusions Under Different Scenarios



TRT: treatment

Plaggio et al. JAMA 2012;308(24):2594-2604

Adverse Events

Adverse Events	FOLFOX 3m Arm	FOLFOX 6m Arm	FOLFOX p-value[1]	CAPOX 3m Arm	CAPOX 6m Arm	CAPOX p-value[1]
Overall						
G2	70%	89%	<.0001	65%	85%	.0001
G3-4	38%	57%		24%	37%	
Neurotoxicity						
G2	17%	48%	<.000	15%	45%	<.0001
G3-4	3%	10%		3%	3%	
Diarrhea						
G2	11%	13%	<.0001	10%	13%	0.0117
G3-4	5%	7%		7%	9%	

[1]Chi-squared test for trend; Total of 19 grade 6 events; Adverse events only collected on first 817 patients enrolled to SCOT trial

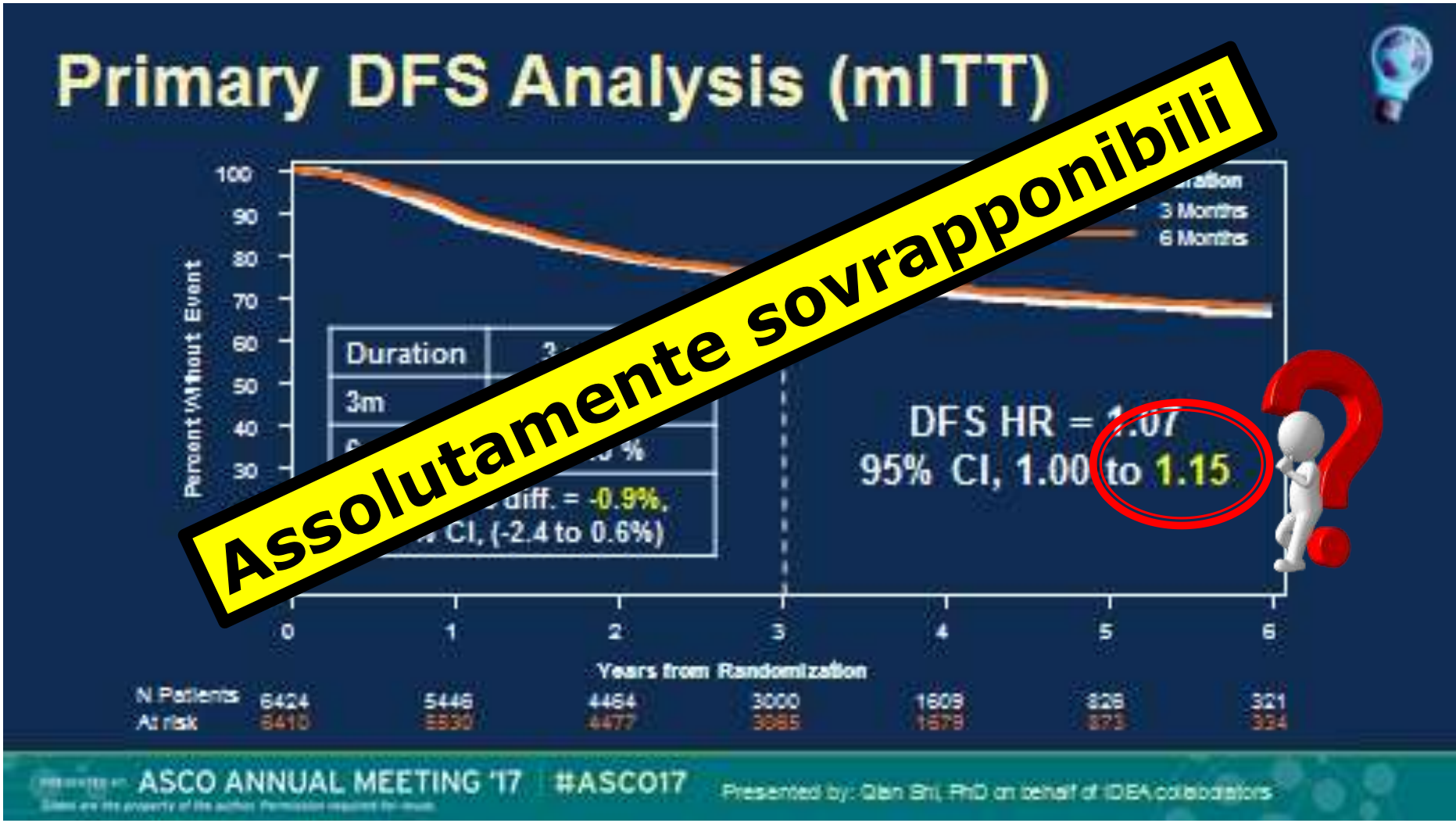
IDEA

Treatment Compliance

Treatment Compliance	FOLFOX 3m Arm	FOLFOX 6m Arm	CAPOX 3m Arm	CAPOX 6m Arm
Total no. weeks received treatment Median (Q1-Q3)	12 (12-12)	24 (20-24)	12 (12-12)	24 (18-24)
Reached the planned last cycle[1]	90%	71%	86%	65%
% of dose actually delivered, Mean (Standard Deviation)				
5FU[2]	92.4 (22.7)	81.6 (26.6)	---	---
Capecitabine	---	---	91.2 (23.5)	78.0 (29.4)
Oxaliplatin	91.4 (19.9)	72.8 (25.6)	89.8 (21.7)	69.3 (28.3)

[1] 1% of patients assigned to 3m treatment (both FOLFOX and CAPOX) received > 3m of treatment; [2] combining infusion and bolus

IDEA


Primary DFS Analysis (mITT)
Assolutamente sovrapponibili
Percent Without Event
100
90
80
70
60
50
40
30
3 Months
6 Months
Duration
3m
diff. = -0.9%,
CI, (-2.4 to 0.6%)
DFS HR =
95% CI, 1.00 to 1.15
0
1
2
3
4
5
6
Years from Randomization
N Patients
At risk
6424
5446
4464
3000
1609
826
321
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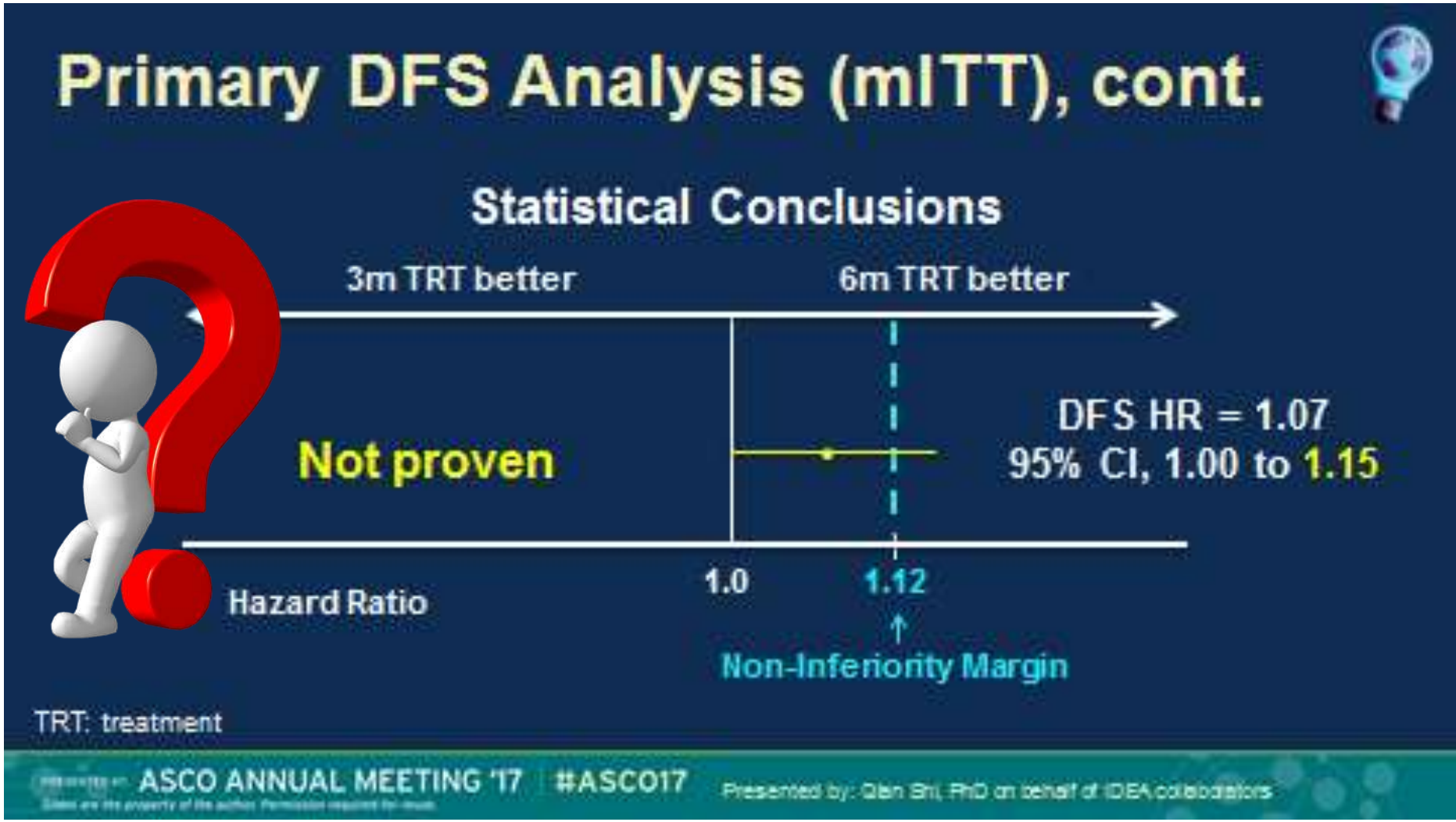
IDEA


Primary DFS Analysis (mITT), cont.
Statistical Conclusions
3m TRT better
6m TRT better
Not proven
DFS HR = 1.07
95% CI, 1.00 to 1.15
1.0
1.12
Hazard Ratio
Non-Inferiority Margin
TRT: treatment
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Presented by: Qian Shi, PhD on behalf of IDEA collaborators

Quale impatto per le linee guida ?

IDEA

- **Studio negativo → Nessuno**

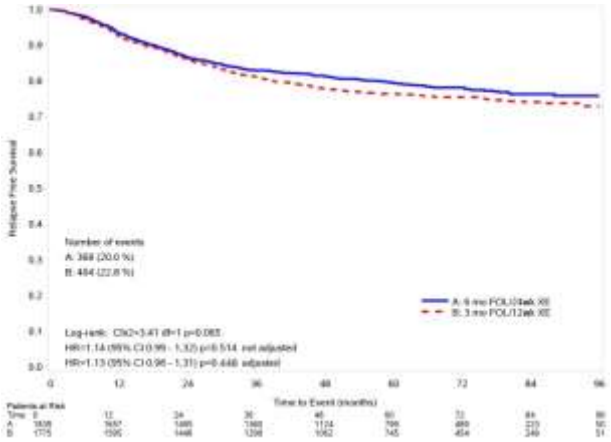
- **Differenza DFS a 3 aa clinicamente irrilevante (0,9%) → Practice changing**

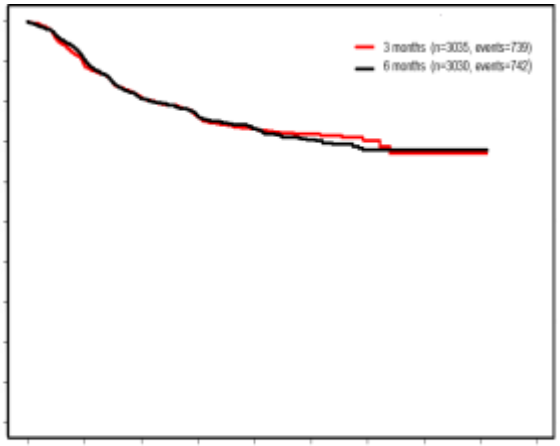
- **Troppo presto**

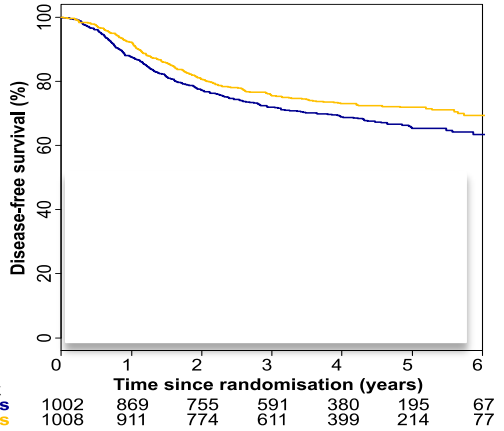
Qualità delle evidenze

- **Study design - errori nella pianificazione e conduzione dello studio**
- **Precision - precisione delle stime**
- **Indirectness - diretta applicabilità delle evidenze (P.I.C.O.)**
- **Consistency - coerenza dei risultati tra studi differenti**
- **Publication bias - pubblicazione selettiva dei dati**

Results: RFS/DFS Overall Population







Presented by: Jeffrey Meyerhardt, MD, MPH

Duration	TOSCA (3 yr RFS)	SCOT (3 yr DFS) (Colon and Re m)	IDEA-France (3 yr DFS)
3m	81.1%		
6m			
HR (6 is referent)	1.31)	007-1.113)	24 (1.05-1.46)
3 yr DFS Δ	-1.9%	-0.4%	4%

Non inferiority **Not** **Proven** (upper margin >1.2)

Non inferiority **Proven** (upper margin <1.13)

Inferiority Demonstrated

IDEA

Trial	pazienti	schema	%	caratteristiche
SCOT				retto
TOSCA	2402	XELOX o FOLFOX4	19	III, colon
IDEA France				
ACHIEVE	1291	CAPOX o mFOLFOX6	10	III, asiatici
C80702				
HORG		FOLFOX4		

L'unico studio non inferiore pesa per un terzo

L'unico studio che evidenzia inferiorità pesa solo un sesto

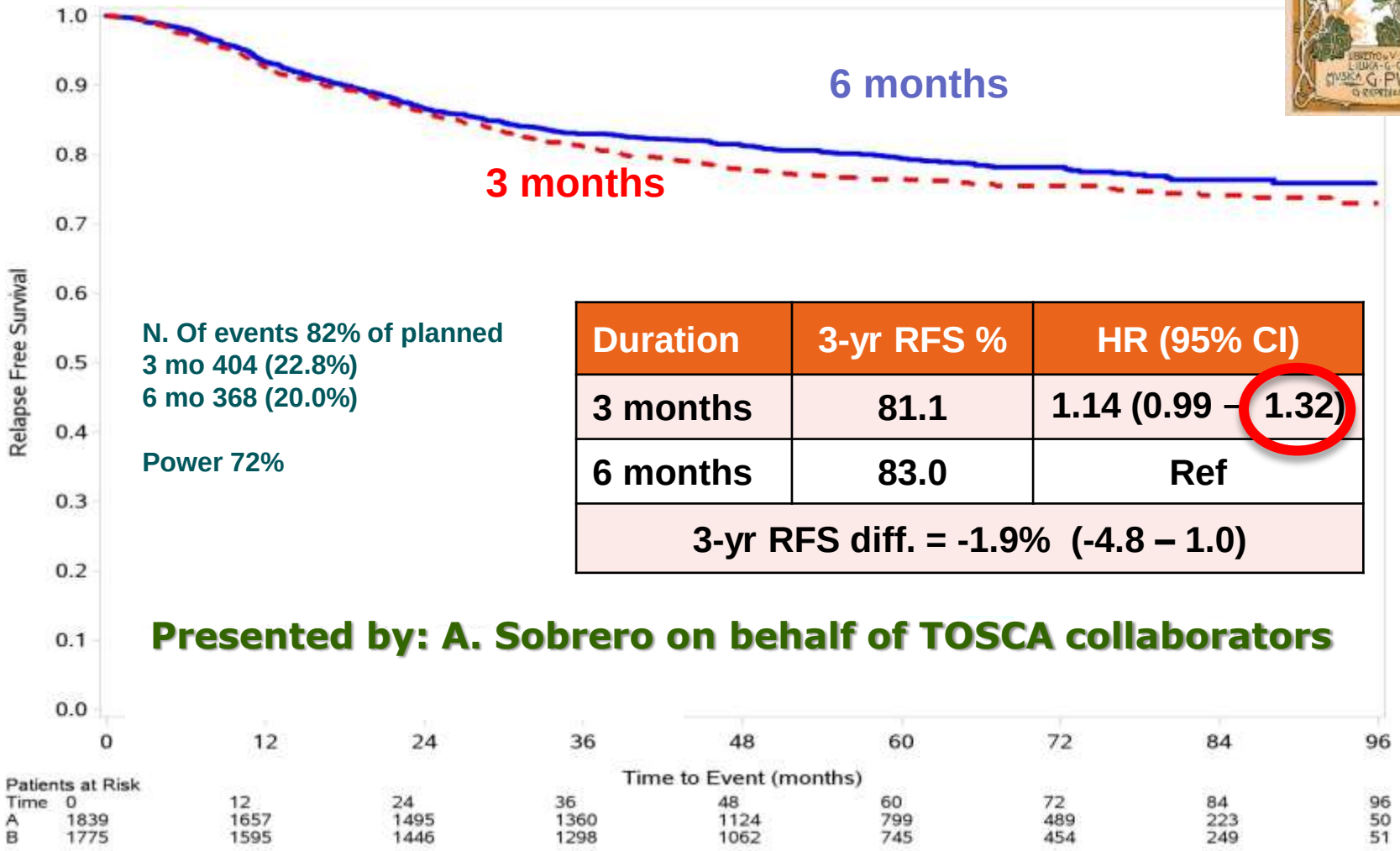
Nessuna informazione su un quarto dei pazienti

Indirectness – diretta applicabilità delle evidenze (P.I.C.O.)

- **popolazione, intervento, controllo o outcome indiretti: il quesito per il quale si intende porre la raccomandazione si riferisce a una popolazione, intervento, controllo o outcome diversi da quelli per i quali sono disponibili prove di efficacia in letteratura**

- **I «nostri pazienti» sono quelli rappresentati dallo studio TOSCA i cui dati non sono così convincenti**

Results: RFS by arm Overall Population



N. Of events 82% of planned
3 mo 404 (22.8%)
6 mo 368 (20.0%)

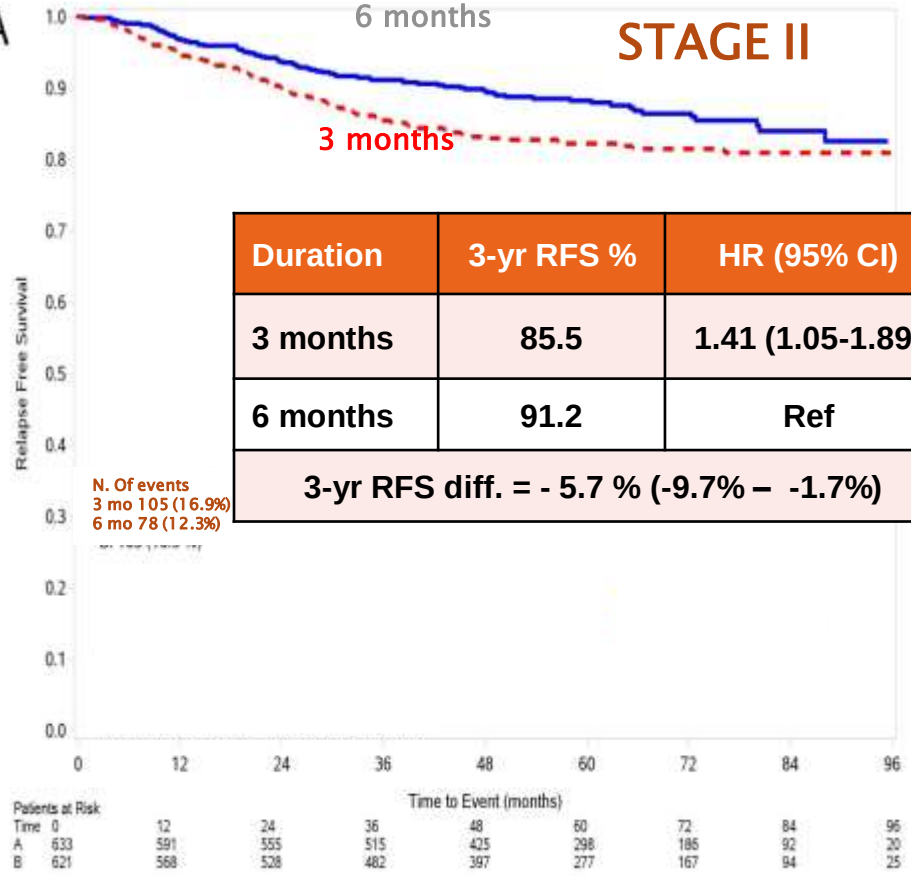
Power 72%

Duration	3-yr RFS %	HR (95% CI)
3 months	81.1	1.14 (0.99 – 1.32)
6 months	83.0	Ref
3-yr RFS diff. = -1.9% (-4.8 – 1.0)		

Presented by: A. Sobrero on behalf of TOSCA collaborators

Results: RFS by stage

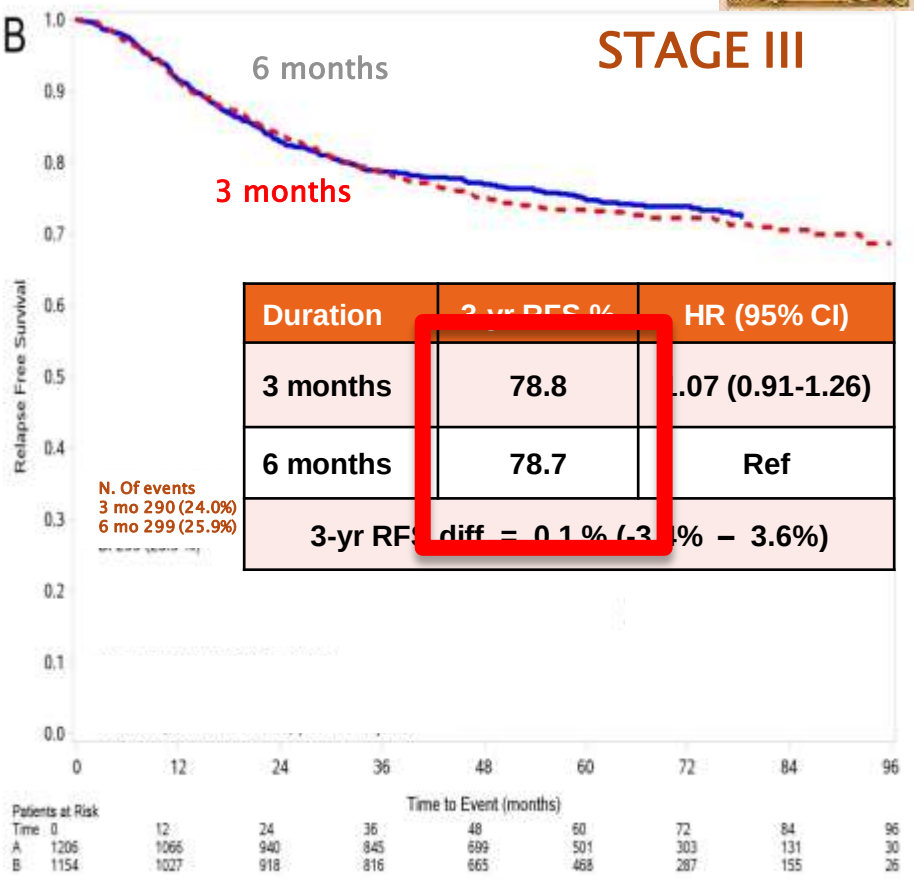
A



STAGE II

Duration	3-yr RFS %	HR (95% CI)
3 months	85.5	1.41 (1.05-1.89)
6 months	91.2	Ref
3-yr RFS diff. = - 5.7 % (-9.7% – -1.7%)		

B



STAGE III

Duration	3-yr RFS %	HR (95% CI)
3 months	78.8	1.07 (0.91-1.26)
6 months	78.7	Ref
3-yr RFS diff. = 0.1 % (-3.4% – 3.6%)		

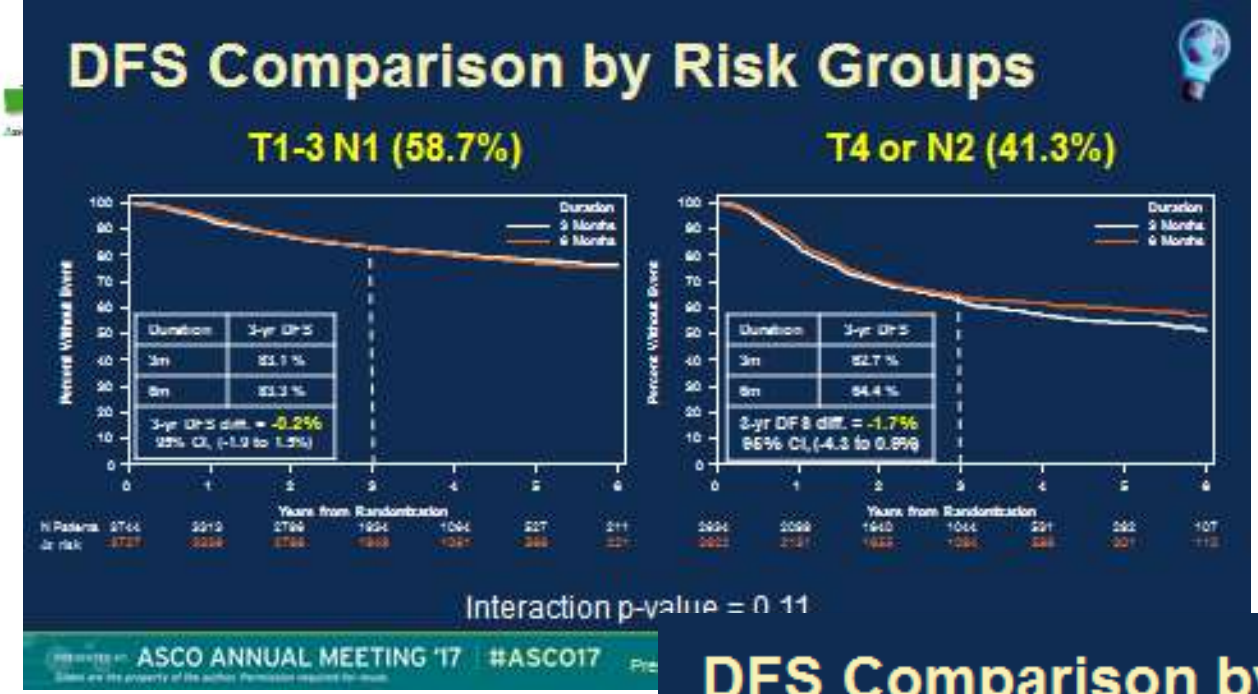
Presented by: A. Sobrero on behalf of TOSCA collaborators

Quale impatto per le linee guida

IDEA

- **Significato delle analisi di sottogruppo non pre-pianificate**
  - **Generatrici di ipotesi**

DFS Comparison by Risk Groups



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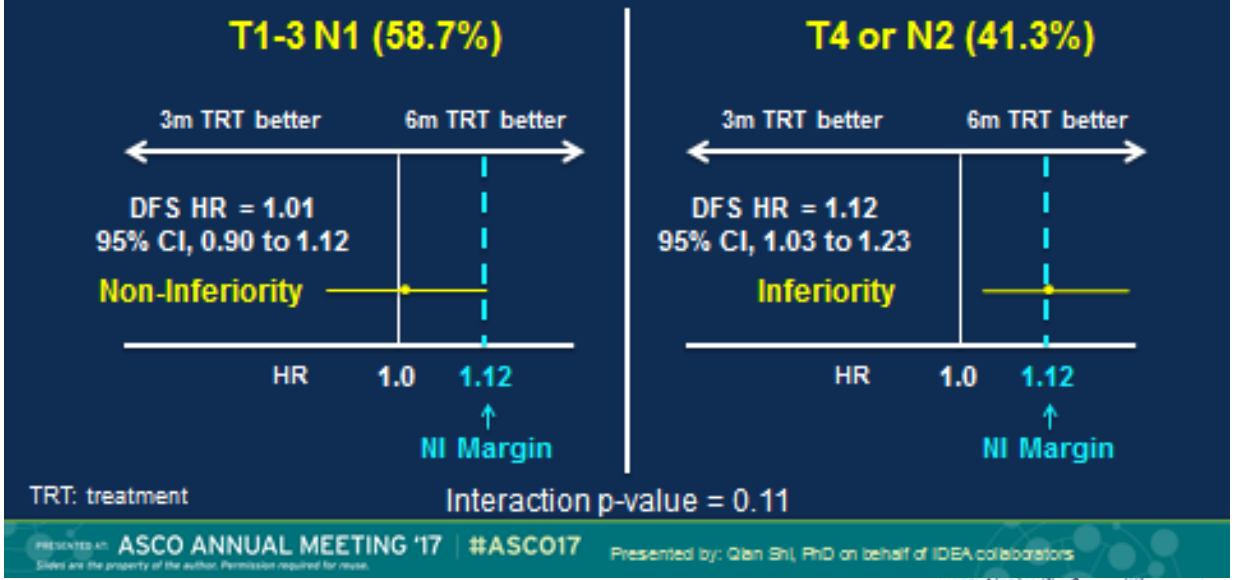
DFS Comparison by Risk Groups, cont.



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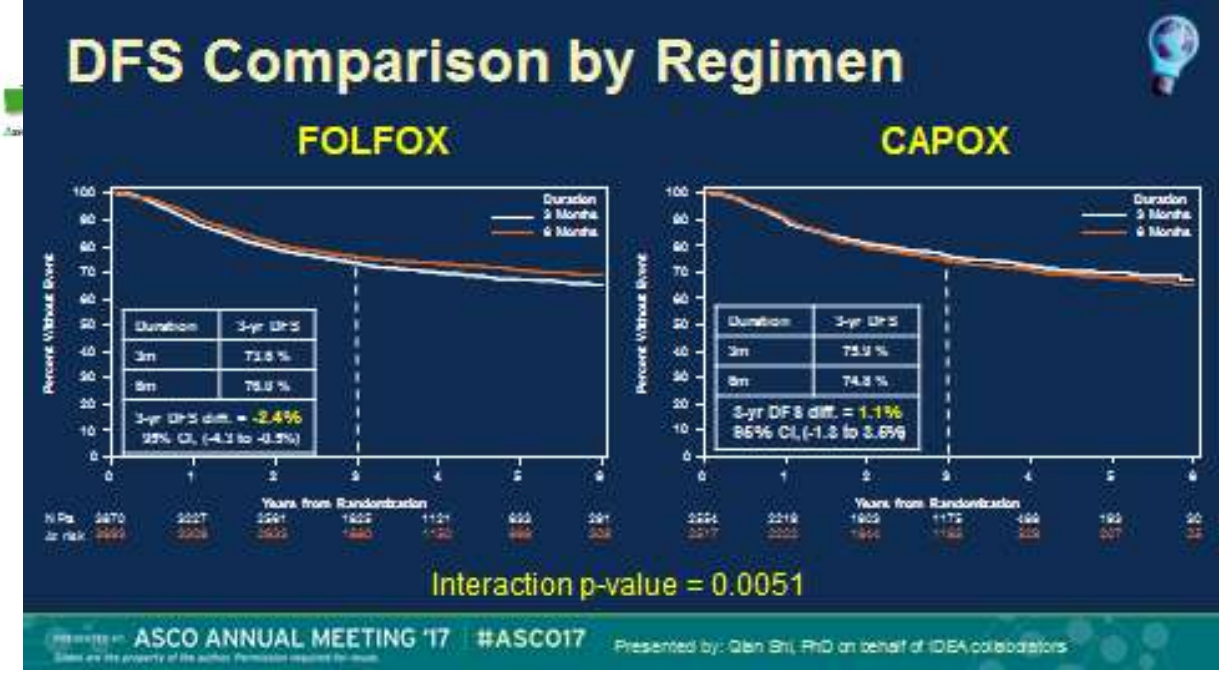
DFS Comparison by Regimen
FOLFOX
CAPOX
Duration
3 Months
6 Months
Years from Randomization
Interaction p-value = 0.0051
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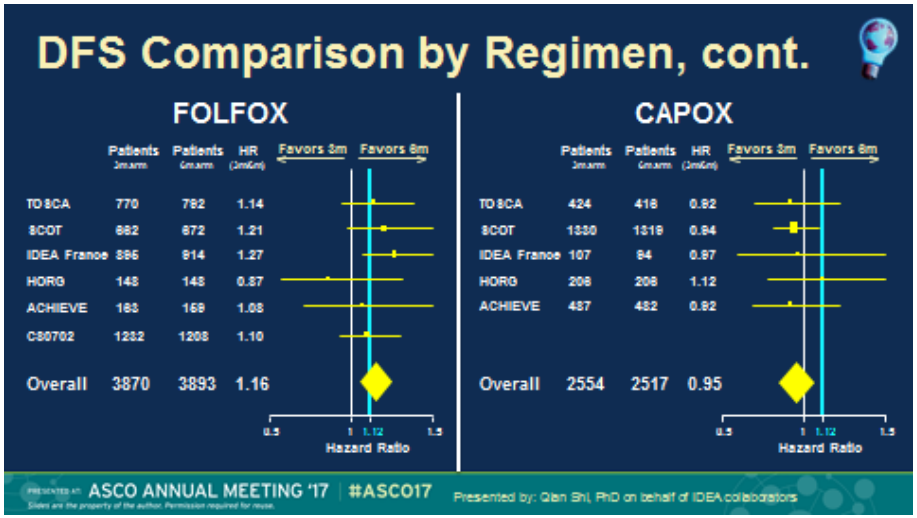
Presented by: Qian Shi, PhD on behalf of IDEA collaborators

IDEA


DFS Comparison by Regimen, cont.
FOLFOX
CAPOX
Patients 3m arm
Patients 6m arm
HR (3m/6m)
Favors 3m
Favors 6m
TOSCA 770 782 1.14
SCOT 882 872 1.21
IDEA France 896 914 1.27
HORG 148 148 0.87
ACHIEVE 168 169 1.08
C80702 1252 1208 1.10
Overall 3870 3893 1.16
TOSCA 424 418 0.92
SCOT 1330 1319 0.94
IDEA France 107 94 0.97
HORG 208 208 1.12
ACHIEVE 487 482 0.92
Overall 2554 2517 0.95
Hazard Ratio
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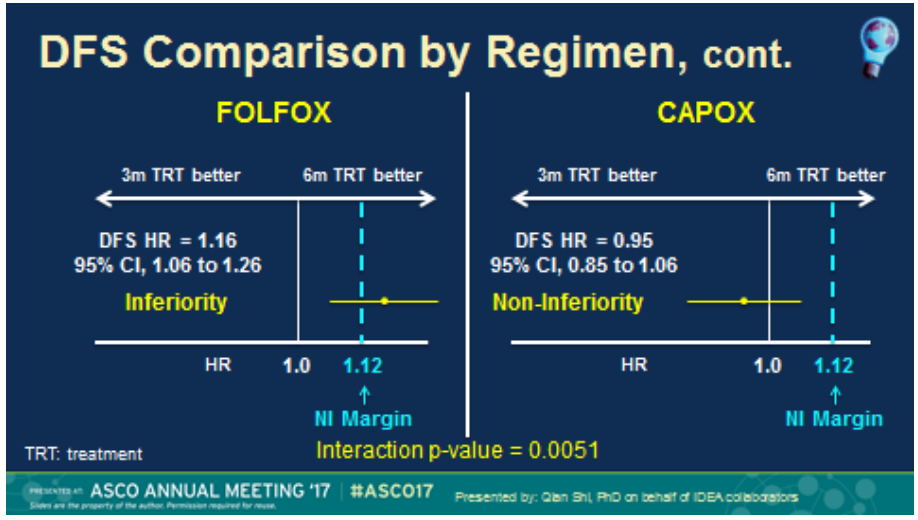
DFS Comparison by Regimen, cont.
FOLFOX
CAPOX
3m TRT better
6m TRT better
DFS HR = 1.16
95% CI, 1.06 to 1.26
Inferiority
DFS HR = 0.95
95% CI, 0.85 to 1.06
Non-Inferiority
HR
1.0
1.12
NI Margin
TRT: treatment
Interaction p-value = 0.0051
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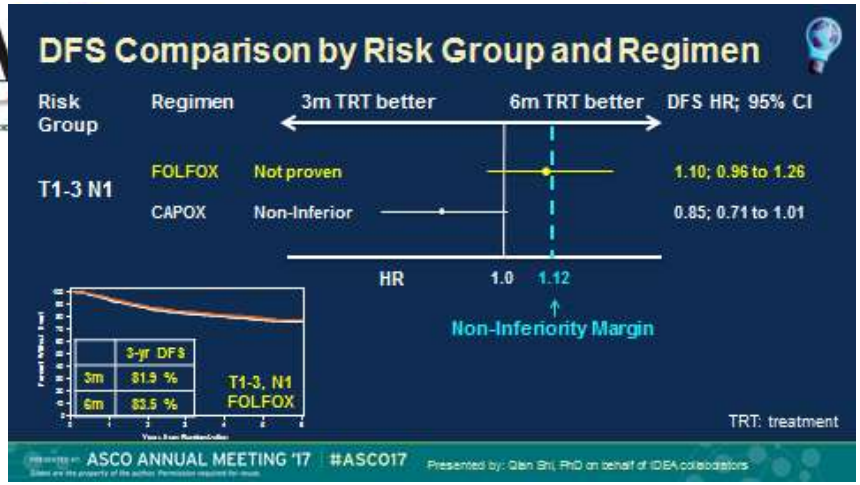
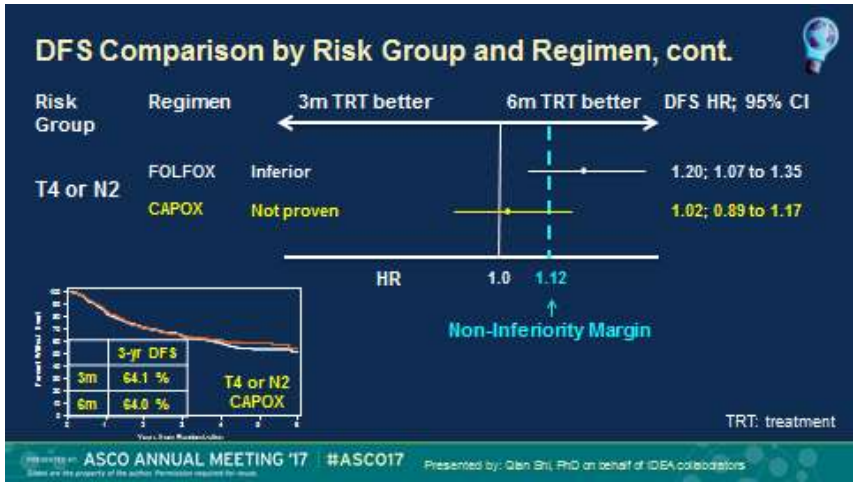
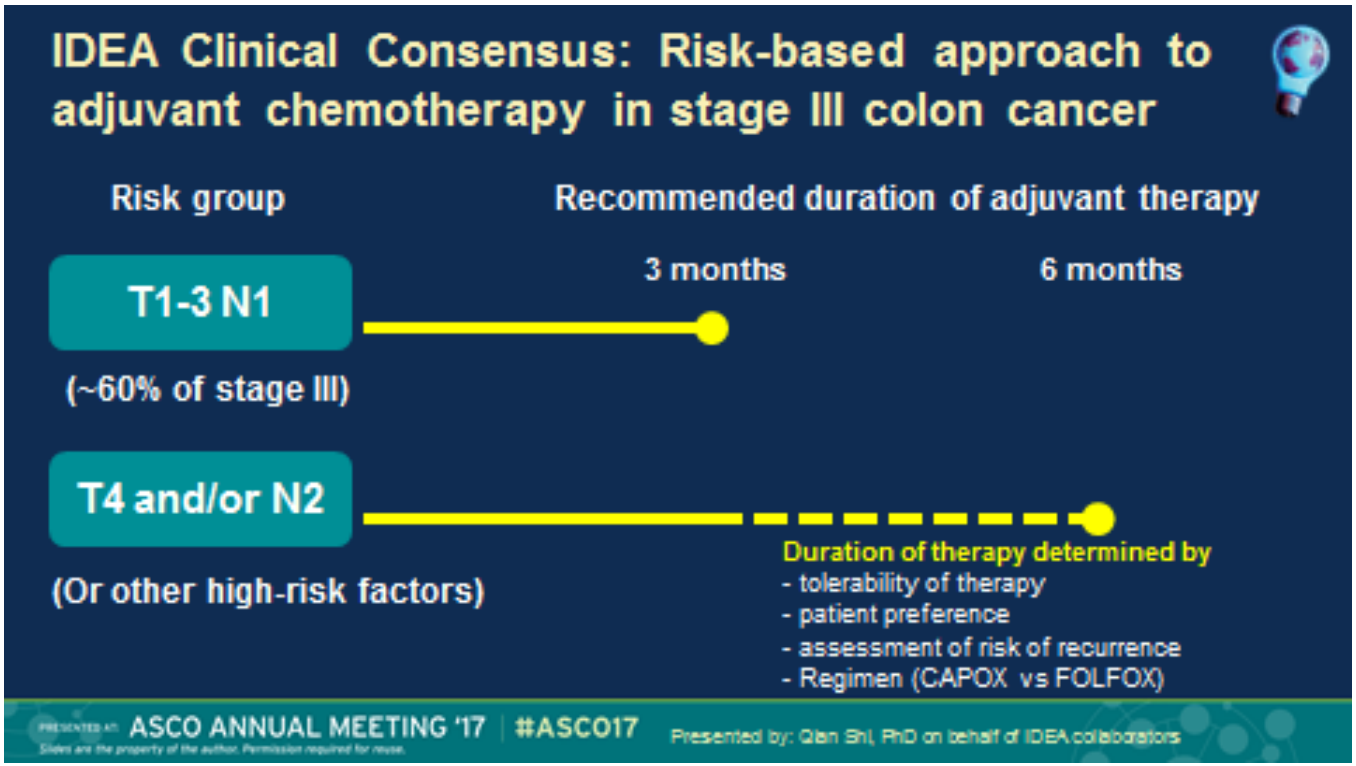
Presented by: Qian Shi, PhD on behalf of IDEA collaborators

3 yr DFS rate (%) and HR by regimen and risk group		Regimen								
		CAPOX			FOLFOX			CAPOX/FOLFOX combined		
		3 yr DFS, % (95% CI)		*HR (95% CI)*	3 yr DFS, % (95% CI)		*HR (95% CI)*	3 yr DFS, % (95% CI)		*HR (95% CI)*
		3 m	6 m		3 m	6 m		3 m	6 m	
Risk group	Low-risk (T1-3 N1) ~60%	85.0 (83.1-86.9)	83.1 (81.1-85.2)	*0.85 (0.71-1.01)*	81.9 (80.2-83.6)	83.5 (81.9-85.1)	*1.10 (0.96-1.26)*	83.1 (81.8-84.4)	83.3 (82.1-84.6)	*1.01 (0.90-1.12)*
	High-risk (T4 and / or N2) ~40%	64.1 (61.3-67.1)	64.0 (61.2-67.0)	*1.02 (0.89-1.17)*	61.5 (58.9-64.1)	64.7 (62.2-67.3)	*1.20 (1.07-1.35)*	62.7 (60.8-64.4)	64.4 (62.6-66.4)	*1.12 (1.03-1.23)*
	Risk groups combined	75.9 (74.2-77.6)	74.8 (73.1-76.6)	*0.95 (0.85-1.06)*	73.6 (72.2-75.1)	76.0 (74.6-77.5)	*1.16 (1.06-1.26)*	P-value interaction test: Regimen: 0.0061 Risk group: 0.11		

Non-inferior | Not proven | Inferior


DFS Comparison by Risk Group and Regimen
Risk Group
Regimen
3m TRT better
6m TRT better
DFS HR; 95% CI
T1-3 N1
FOLFOX
Not proven
1.10; 0.96 to 1.26
CAPOX
Non-Inferior
0.85; 0.71 to 1.01
HR
1.0
1.12
Non-Inferiority Margin
3-yr DFS
3m 81.9 %
6m 83.5 %
T1-3, N1 FOLFOX
TRT: treatment
ASCO ANNUAL MEETING '17 | #ASCO17
Presented by: Qian Shi, PhD on behalf of IDEA collaborators


DFS Comparison by Risk Group and Regimen, cont.
Risk Group
Regimen
3m TRT better
6m TRT better
DFS HR; 95% CI
T4 or N2
FOLFOX
Inferior
1.20; 1.07 to 1.35
CAPOX
Not proven
1.02; 0.89 to 1.17
HR
1.0
1.12
Non-Inferiority Margin
3-yr DFS
3m 64.1 %
6m 64.0 %
T4 or N2 CAPOX
TRT: treatment
ASCO ANNUAL MEETING '17 | #ASCO17
Presented by: Qian Shi, PhD on behalf of IDEA collaborators


IDEA Clinical Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer
Risk group
Recommended duration of adjuvant therapy
3 months
6 months
T1-3 N1
(~60% of stage III)
T4 and/or N2
(Or other high-risk factors)
Duration of therapy determined by
- tolerability of therapy
- patient preference
- assessment of risk of recurrence
- Regimen (CAPOX vs FOLFOX)
ASCO ANNUAL MEETING '17 | #ASCO17
Presented by: Qian Shi, PhD on behalf of IDEA collaborators

IDEA

GOOD IDEA

OR

Raccomandazione 2017

- **Con i dati disponibili lo standard dovrebbe rimanere 6 mesi (FOLFOX o CAPOX)**
- **Nei pazienti a basso rischio può essere considerato, in caso di tossicità, sospendere dopo 3 mesi**
- **In alternativa perchè escludere, nei bassi rischi, la sola fluoropirimidina per 6 mesi?**

IDEA

….the non-inferiority of a 3-month duration of therapy, as compared with a 6-month duration, was not confirmed. However, the results were strongly affected by the selected treatment and risk group. In patients treated with CAPOX, 3 months of therapy was as effective as 6 months, particularly in thelower-risk subgroup. In patients treated with FOLFOX, 6 months of therapy resulted in a higher rate of disease-free survival, particularly in the high-risk subgroup.
These data suggest that the choice of treatment regimen, duration of therapy, and characteristics of the patients may be balanced against the substantial risk of increased toxicity of longer oxaliplatin-based therapy, including persistent neurotoxicity.

In conclusion, TOSCA was not able to demonstrate that 3 months of oxaliplatin-based adjuvant treatment is as efficacious as 6 months (technically 3 months were not noninferior to six months). The results depended on the adjuvant regimen and risk.
For patients treated with CAPOX, 3 months were as good as 6 months; for FOLFOX, 6 months added extra benefit.
Counterintuitively, the low-risk patients benefitted more than the high-risk population from the 6-month duration. The choice of regimen and duration should depend on patient characteristics and be balanced against the extra toxicity of longer therapy, particularly, persistent chronic neurotoxicity. Because the results of TOSCA on substages are counterintuitive, they should be interpreted with caution within the context of the combined analyses of IDEA.

IDEA France

…the superior DFS of 6-month adjuvant treatment compared with 3 months, especially in patients with T4 and/or N2 colon cancer. This finding is in agreement with DFS HR data from the overall analysis of patients who received FOLFOX in the international IDEA collaboration.
These results should be integrated, discussed, and considered alongside the international IDEA collaboration data.

Articles

3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial

Summary

Background 6 months of oxaliplatin-containing chemotherapy is usually given as adjuvant treatment for stage 3 colorectal cancer. We investigated whether 3 months of oxaliplatin-containing chemotherapy would be non-inferior to the usual 6 months of treatment.

Methods The SCOT study was an international, randomised, phase 3, non-inferiority trial done at 244 centres. Patients aged 18 years or older with high-risk stage II and stage III colorectal cancer underwent central randomisation with minimisation for centre, choice of regimen, sex, disease site, N stage, T stage, and the starting dose of capecitabine. Patients were assigned (1:1) to receive 3 months or 6 months of adjuvant oxaliplatin-containing chemotherapy. The chemotherapy regimens could consist of CAPOX (capecitabine and oxaliplatin) or FOLFOX (bolus and infused fluorouracil with oxaliplatin). The regimen was selected before randomisation in accordance with choices of the patient and treating physician. The primary study endpoint was disease-free survival and the non-inferiority margin was a hazard ratio of 1·13. The primary analysis was done in the intention-to-treat population and safety was assessed in patients who started study treatment. This trial is registered with ISRCTN, number ISRCTN59757862, and follow-up is continuing.

Findings 6088 patients underwent randomisation between March 27, 2008, and Nov 29, 2013. The intended treatment was FOLFOX in 1981 patients and CAPOX in 4107 patients. 3044 patients were assigned to 3 month group and

The study achieved its primary endpoint of showing that 3 months of oxaliplatin-containing adjuvant chemotherapy is non-inferior to 6 months of the same treatment in the overall trial population.
3 months of treatment might therefore be considered a new standard of care for adjuvant chemotherapy, especially if CAPOX is to be given.

Introduction

NEW STANDARD

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Open Access | Original research

Safety data from the phase III Japanese ACHIEVE trial: part of an international, prospective, planned pooled analysis of six phase III trials comparing 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer

Masahito Kotaka,[1] Takeharu Yamanaka,[2] Takayuki Yoshino,[3] Dai Manaka,[4] Tetsuya Eto,[5] Junichi Hasegawa,[6] Akinori Takagane,[7] Masato Nakamura,[8] Takeshi Kato,[9] Yoshinori Munemoto,[10] Fumitaka Nakamura,[11] Hiroyuki Bando,[12] Hiroki Taniguchi,[13] Makio Gamoh,[14] Manabu Shiozawa,[15] Shigetoyo Saji,[16] Yoshihiko Maehara,[17] Tsunekazu Mizushima,[18] Atsushi Ohtsu,[3] Masaki Mori[18]

Received 9 March 2018
Revised 2 April 2018
Accepted 3 April 2018

ABSTRACT

Background The International Duration Evaluation of Adjuvant chemotherapy project investigated whether a shorter duration of oxaliplatin-based adjuvant chemotherapy was as effective as 6 months of identical chemotherapy for resected stage III colon cancer. As part of this project, we report safety data from the Japanese ACHIEVE study (JFMC47-1202-C3).

Patients and methods ACHIEVE was an open-label, multicentre trial randomising patients with stage III colon cancer to receive 3 m or 6 m of mFOLFOX6/CAPOX after surgery. Choice of regimen was declared before randomisation by a site investigator.

Results Between August 2012 and June 2014, 1313 patients were enrolled and, of those, 1277 were analysed for the safety analysis, with 635 in arm 6 (mFOLFOX6, n=158; CAPOX, n=477) and 642 in arm 3 (mFOLFOX6, n=161; CAPOX, n=481). Grade 3 or worse peripheral sensory neuropathy (PSN) developed in 5%/0.6% of patients receiving mFOLFOX6 in arm 6/3 (p=0.019) and 6%/1% of those receiving CAPOX in arm 6/3 (p<0.001). Similarly, grade 2 or worse PSN developed in 36%/11% of patients receiving mFOLFOX6 in arm 6/3 (p<0.001) and 37%/14% of those receiving CAPOX in arm 6/3 (p<0.001). An association between baseline creatinine clearance (CCr) and adverse events (AEs) was found that patients with CAPOX were significantly more likely to develop AEs ≥grade 3 when they had a CCr ≤50 (OR 1.67; p=0.048).

Conclusions We confirmed in the Japanese population that the shorter duration of adjuvant chemotherapy resulted in a significant reduction of PSN. In patients with CAPOX, renal function was significantly related to severe AEs.

Trial registration number UMIN000008543; Results.

Key questions

What is already known about this subject?
- Six months of FOLFOX or CAPOX are positioned as the standard adjuvant chemotherapy regimens for treatment of stage III colon cancer.
- Peripheral sensory neuropathy (PSN) is an important dose-limiting toxicity of oxaliplatin therapy, so shorter duration of adjuvant FOLFOX or CAPOX therapy would be beneficial for patients if efficacy was not reduced.

What does this study add?
- We have demonstrated that shorter duration of adjuvant chemotherapy resulted in a significant reduction of PSN.
- This study was the only investigation in the International Duration Evaluation of Adjuvant chemotherapy (IDEA) project performed for the Asian population. There was a somewhat lower incidence of PSN related to oxaliplatin therapy in Asian patients, but a level of reduction in PSN frequency was consistent among the IDEA studies.
- We have demonstrated that in patients with CAPOX, renal function was significantly related to severe adverse events.

How might this impact on clinical practice?
- Our data support the importance of careful selection of starting dose of capecitabine in patients with a renal impairment receiving CAPOX therapy.

INTRODUCTION

Colorectal cancer is the third most frequent cancer worldwide and the third highest cause of cancer-related deaths.[1] Surgical resection is the only curative treatment for colorectal cancer and postoperative adjuvant chemotherapy, including oxaliplatin-based therapy,

Kotaka M, et al. ESMO Open 2018;3:e000354. doi:10.1136/esmoopen-2018-000354

Solo dati di tossicità

Oncologia Medica HUMANITAS GAVAZZENI

Is this an important question?

- **Almeno 18 articoli tra editoriali, commenti, revisioni, ecc. da marzo 2018 sull'argomento**
- **2 sessioni speciali ESMO**
- **2 sessioni educazionali ASCO**
- **Dibattito in quasi tutti i convegni sul colon**
- **Oxford debate all'AIOM**
- **Linee guida AIOM con valutazione Grade**

È un quesito importante?

- **Differenza assoluta tra 3 mesi e 6 mesi 0,9% (C.I.: +0,6; –2,4)**
- **ARR 0,9% →0,009**
- **NNT 1/ARR → 1/0,009 → 111 (1/0.024 → 41)**
- **30 pts ogni 100 avranno neurotossicità senza beneficio**

- **Benefici per il sistema sanitario**
  - **Minor spese di trattamento**
  - **Minori spese per gestione effetti collaterali**
  - **Minori spese di personale e spazi**
- **Rischi**
  - **Il paziente che non recidiva è guarito → peggioramento della sopravvivenza**

Adiuvante
3 vs 6

VOLUME 36 · NUMBER 15 · MAY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 | MARCH 29, 2018 | VOL. 378 NO. 13

Duration of Adjuvant Chemotherapy for Stage III Colon Cancer

A. Grothey, A.F. Sobrero, A.F. Shields, T. Yoshino, J. Paul, J. Taieb, J. Souglakos, Q. Shi, R. Kerr, R. Labianca, J.A. Meyerhardt, D. Vernerey, T. Yamanaka, I. Boukovinas, J.P. Meyers, L.A. Renfro, D. Niedzwiecki, T. Watanabe,* V. Torri, M. Saunders, D.J. Sargent,* T. Andre, and T. Iveson

International, randomised, phase 3, non-inferiority trial

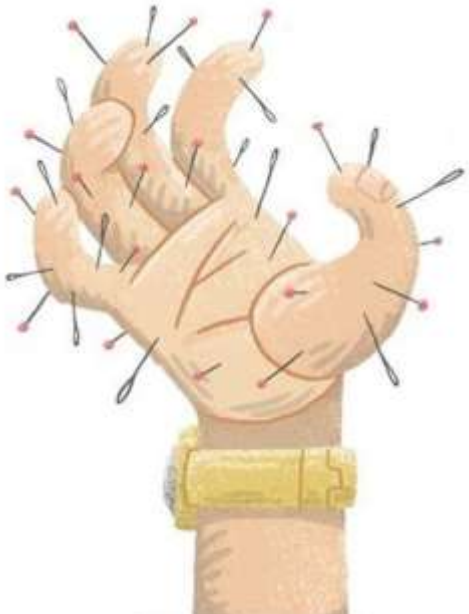
oa

Timothy J Iveson*, Rachel S Kerr*, Mark P Saunders, Jim Cassidy, Niels Henrik Hollander, Josep Tabernero, Andrew Haydon, Bengt Glimelius, Andrea Harkin, Karen Allan, John McQueen, Claire Scudder, Kathleen Anne Boyd, Andrew Briggs, Ashita Waterston, Louise Medley, Charles Wilson, Richard Ellis, Sharadah Essapen, Amandeep S Dhadda, Mark Harrison, Stephen Falk, Sherif Raouf, Charlotte Rees, Rene K Olesen, David Propper, John Bridgewater, Ashraf Azzabi, David Farrugia, Andrew Webb, David Cunningham, Tamas Hickish, Andrew Weaver, Simon Gollins, Harpreet S Wasan, James Paul

Adiuvante 3 vs 6
Impatto su NEUROTOX

Neurotox G3-4

- ✓ **Relative Risk > RR=0.18 (0.15-0.22)**
- ✓ **Absolute Risk > 114 fewer per 1.000 (from 108 fewer to 118 fewer)**



Impatto in termini di RISPARMIO di TOX <u>a favore dei 3 mesi</u> vs 6 mesi: IMPORTANTE

Adiuvante 3 vs 6
Stadio III

DFS

- ✓ **Relative effect > HR=1.07 (1.00-1.15)**
- ✓ **Absolute effect > 15 more per 1.000 (from 0 fewer to 31 more)**

Non provata non inferiorita' dei 3 mesi vs i 6 mesi in termini di DFS

VOTAZIONI

Bilancio beneficio/danno

- ✓ ***Incerto: 6***
- ✓ **A favore dei 3 mesi: 4**

Forza della raccomandazione

- ✓ ***Negativa debole: 8***
- ✓ **Positiva debole: 2**

Adiuvante 3 vs 6
Stadio III

Qualità dell'evidenza GRADE	Raccomandazione	Forza della raccomandazione clinica
Moderata	Nei pazienti con tumore del colon in stadio III nel loro complesso una chemioterapia adiuvante a base di oxaliplatino delle durata di 3 mesi non dovrebbe essere considerata come opzione di prima intenzione; essa potrebbe comunque essere suscettibile di impiego in casi selezionati sulla base del livello di rischio in relazione allo stadio e dello specifico regime da utilizzare, previa completa condivisione con il paziente (38).	**Negativa debole**

CT adiuvante oxa-based di 3 mesi
NON dovrebbe essere presa in considerazione come prima opzione

Adiuvante 3 vs 6
Stadio III pT1-3 pN1

DFS

- ✓ **Relative effect > HR=1.01 (0.90-1.12)**
- ✓ **Absolute effect > 2 more per 1.000 (from 16 fewer to 19 more)**

Possibile (ipotesi) non inferiorita'
dei 3 mesi vs i 6 mesi in termini di DFS

NO impatto sfavorevole dei 3 mesi vs 6 mesi (secondo il Panel)

VOTAZIONI

Bilancio beneficio/danno

- ✓ ***A favore dei 3 mesi: 10***

Forza della raccomandazione

- ✓ ***Positiva debole: 10***

Adiuvante 3 vs 6
Stadio III pT1-3 pN1

Qualità dell'evidenza GRADE	Raccomandazione	Forza della raccomandazione clinica
Moderata	Nei pazienti con tumore del colon pT1-3 pN1 puo' essere presa in considerazione una chemioterapia adiuvante a base di oxaliplatino delle durata di 3 mesi (38).	**Positiva debole**

CT adiuvante oxa-based di 3 mesi
PUO' essere presa in considerazione

Adiuvante 3 vs 6
Stadio III pT4 e/o pN2

DFS

- ✓ **Relative effect > HR=1.12 (1.03-1.23)**
- ✓ **Absolute effect > 33 more per 1.000 (from 8 more to 61 more)**

Impatto sfavorevole dei 3 mesi vs 6 mesi (secondo il Panel)

VOTAZIONI

Bilancio beneficio/danno

- ✓ **A favore dei 6 mesi: 8**
- ✓ **Probabilmente a favore dei 6 mesi: 2**

Forza della raccomandazione

- ✓ **Negativa forte: 10**

Adiuvante 3 vs 6
Stadio III pT4 e/o pN2

Qualità dell'evidenza GRADE	Raccomandazione	Forza della raccomandazione clinica
Moderata	Nei pazienti con tumore del colon pT4 e/o pN2 una chemioterapia adiuvante a base di oxaliplatino delle durata di 3 mesi non deve essere presa in considerazione come prima opzione. Il trattamento puo' essere interrotto precocemente o depotenziato in caso di insorgenza di tossicita' inaccettabile (38).	**Negativa forte**

CT adiuvante oxa-based di 3 mesi
NON DEVE essere presa in considerazione

Cosa non abbiamo potuto mettere

- **Anti Her2**
- **immunoterapia**

Heracles

	Patients given trastuzumab and lapatinib (n=27)
Complete response	1 (4%, −3 to 11)
Partial response	7 (26%, 9 to 43)
Stable disease ≥16 weeks*	8 (30%, 13 to 47)
Stable disease <16 weeks	4 (15%, 1 to 27)
Objective response	8 (30%, 14 to 50)
Disease control†	16 (59%, 39 to 78)
Duration of response (weeks)	38 (24 to 94+)
Time to response (weeks)	8 (3 to 16)

Data are n (%, 95% CI) or median (range). Response data are best response according to RECIST 1.1. RECIST=Response Criteria Evaluation in Solid Tumors. *Including one unconfirmed partial response according to RECIST 1.1. †Defined as complete plus partial responses plus stable disease >16 weeks.

Table 2: **Responses to treatment**

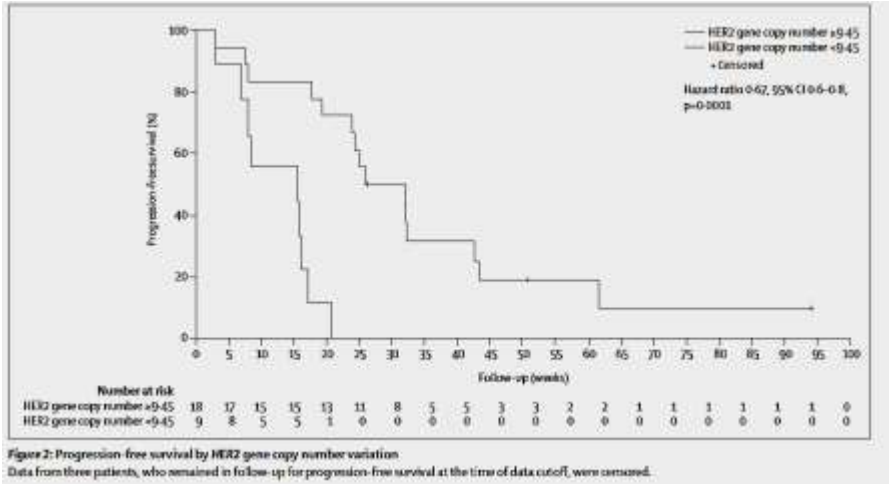
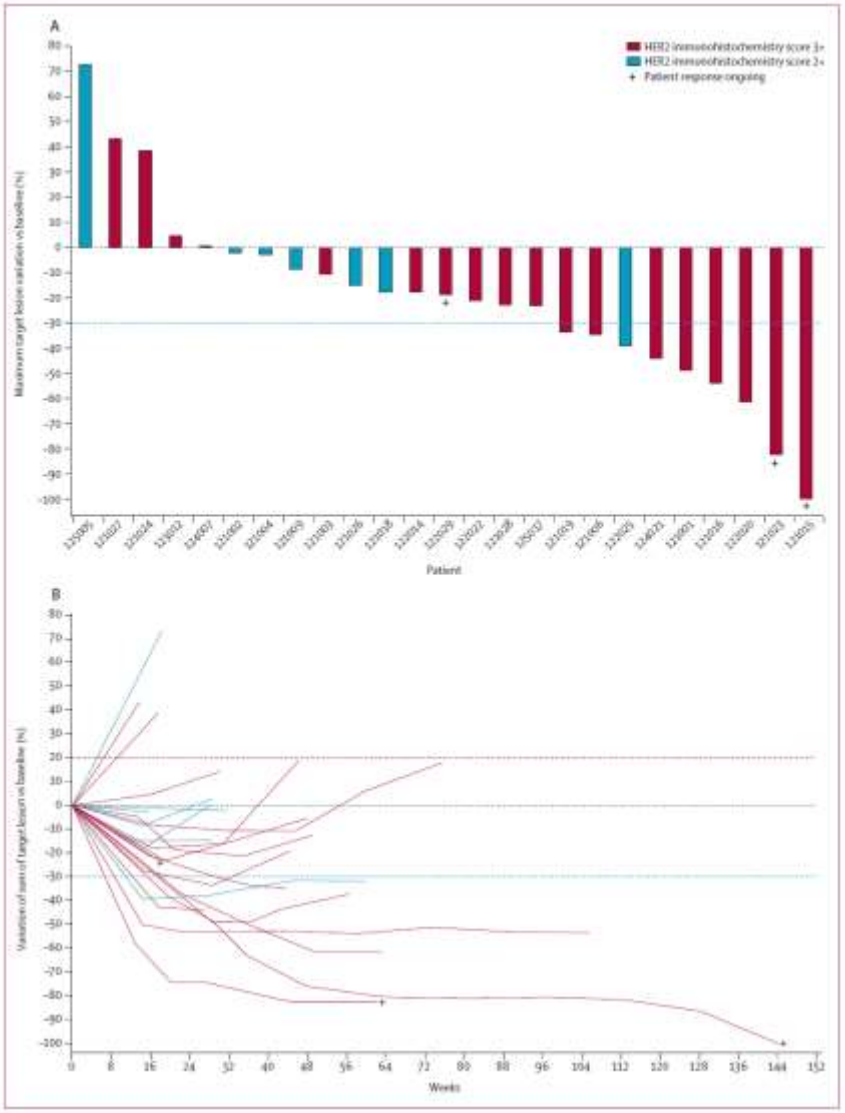


Figure 2: Progression-free survival by HER2 gene copy number variation
Data from three patients, who remained in follow-up for progression-free survival at the time of data cutoff, were censored.



A.Sartore-Bianchi Lancet oncol 2016

Convegno Regionale Aiom Emilia Romagna
Modena 23 novembre 2018

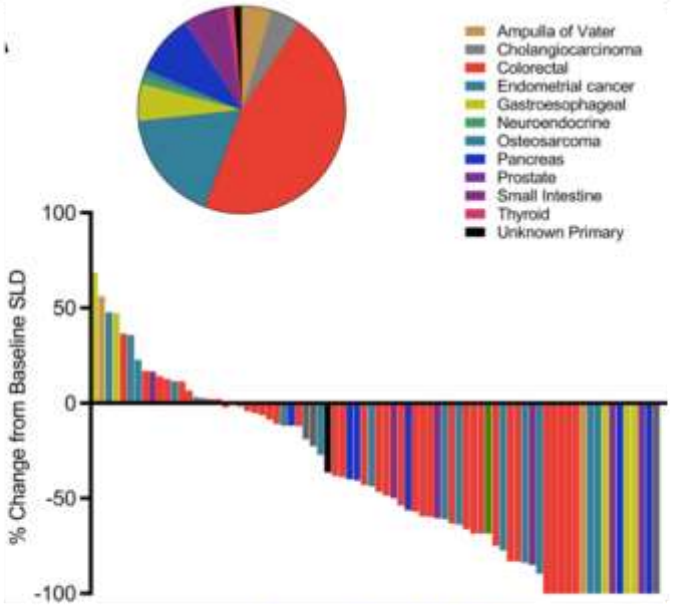
Oncologia Medica HUMANITAS GAVAZZENI

Associazione Italiana di Oncologia Medica

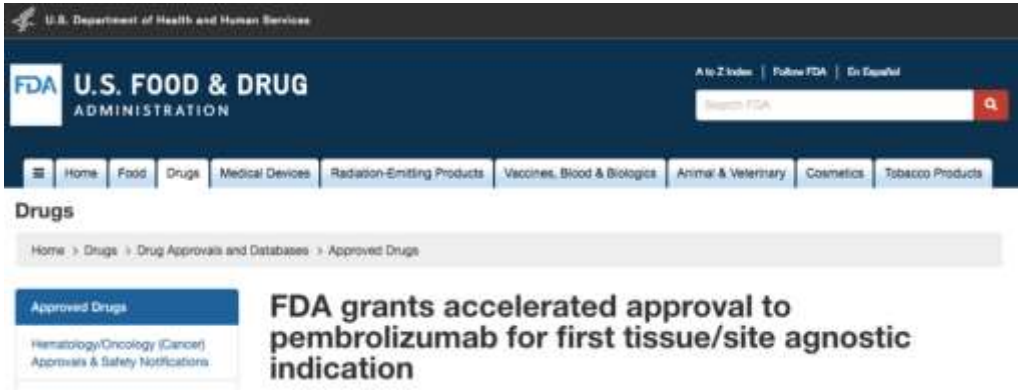
Science REPORTS

Cite as: D. T. Le *et al.*, *Science* 10.1126/science.aan6733 (2017).

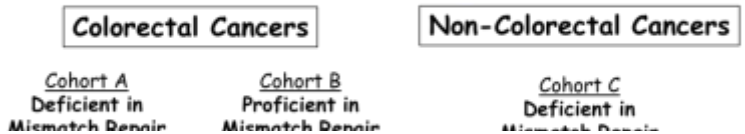
Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade



Le et al, Science 2017



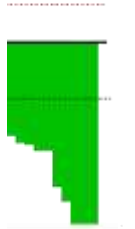
Study Design

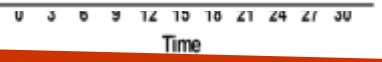


Best Radiographic Response

Study Summary

Type of Response-no (%)	MMR-deficient CRC n=28	MMR-proficient CRC n=25
Objective Response Rate (%)	57%	0%
Disease Control Rate (%)	89%	16%
Progression-free Survival (mos)	Not Reached	2.3
Overall Survival (mos)	Not Reached	5.98

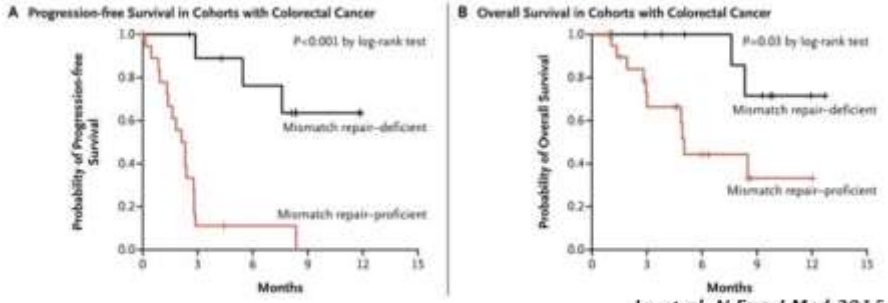




Immunoterapia e MSI

Microsatellite instability & Pembrolizumab

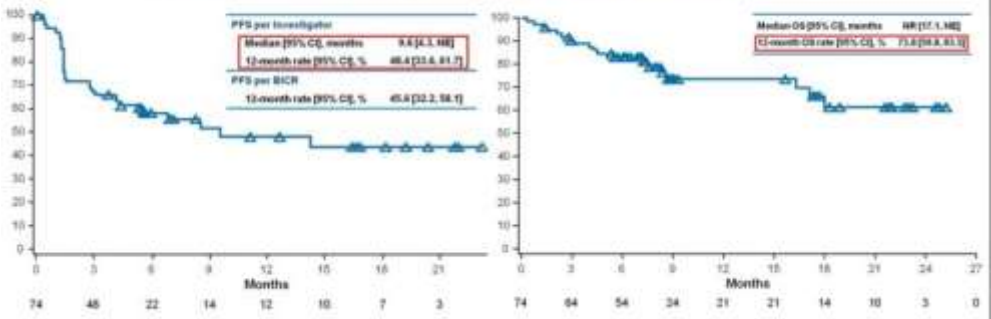
Type of response	MSI (n=10)	MSS (n=18)
Complete Response	0%	0%
Partial Response	40%	0%
Objective Response Rate	40%	0%
Disease Control Rate	90%	11%



Le et al, N Eng J Med 2015

Microsatellite instability & Nivolumab

Patients, n (%)	dMMR/MSI-H per Local Laboratory (N = 74)		dMMR/MSI-H per Central Laboratory (n = 53)	
	Investigator	BICR	Investigator	BICR
ORR, n (%)	23 (31.1)	20 (27.0)	19 (35.8)	17 (32.1)
95% CI	20.8, 42.9	17.4, 38.6	23.1, 50.2	19.9, 46.3
Best overall response, n (%)				
CR	0	2 (2.7)	0	1 (1.8)
PR	23 (31.1)	18 (24.3)	19 (35.8)	16 (30.2)
SD	29 (39.2)	28 (37.8)	21 (39.6)	21 (39.6)
PD	18 (24.3)	20 (27.0)	10 (18.9)	12 (22.6)
Unable to determine	4 (5.4)	6 (11.1)	3 (5.7)	3 (5.7)
Disease control for ≥ 12 weeks, n (%)[a]	51 (68.9)	46 (62.2)	39 (73.6)	37 (69.8)



Overman et al, Lancet Oncol '17

Associazione Italiana di Oncologia Medica

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 January 2018
EMA/51006/2018
EMEA/H/C/003985/II/0030

Withdrawal of the application for a change to the marketing authorisation for Opdivo (nivolumab)

On 13 December 2017, Bristol-Myers Squibb Pharma EEIG officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application to extend the use of Opdivo to treat colorectal cancer.

What is Opdivo?

Opdivo is a cancer medicine that contains the active substance nivolumab and is available as a concentrate that is made up into a solution for infusion (drip) into a vein.

Opdivo has been authorised since June 2015. It is already used for melanoma (a skin cancer), non-small cell lung cancer, renal cell carcinoma (kidney cancer), Hodgkin's lymphoma (cancer affecting lymphocytes, a type of white blood cell), squamous cell cancer of the head and neck, and urothelial cancer (cancer of the bladder and urinary tract). Further information on Opdivo's current uses can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

What was Opdivo expected to be used for?

Opdivo was also expected to be used for the treatment of metastatic colorectal cancer (bowel cancer that has spread to other parts of the body) where the cancer had certain genetic changes (called 'mismatch repair deficient' or 'microsatellite instability high'). It was to be used in adults who had previously been treated with fluoropyrimidines (a type of cancer medicines) together with other cancer medicines.

How does Opdivo work?

The active substance in Opdivo, nivolumab, is a monoclonal antibody, a protein that has been designed to recognise and attach to PD-1, a receptor (target) on cells of the immune system called T cells. Cancer cells can produce proteins (PD-L1 and PD-L2) that attach to this receptor and switch off the activity of the T cells, preventing them from attacking the cancer. By attaching to the receptor,

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Agenzia Italiana del Farmaco
AIFA
Area Pre-Autorizzazione

Roma, 4/05/18

Dott.ssa Stefania Gori
Presidente
Associazione Italiana Oncologia Medica (AIOM)
Via E. Nöe, 23
20133 Milano
aiom.presidente@aiom.it

OGGETTO: Inserimento di nivolumab e pembrolizumab nell'elenco istituito ai sensi della Legge n. 648/96 per il trattamento del carcinoma del colon metastatico con elevata instabilità microsatellitare (MSI-H) pretrattato.

Gentilissima dott.ssa Gori,

in riferimento alla Sua richiesta come da oggetto, Le comunico che la Commissione Consultiva Tecnico-Scientifica (CTS) dell'AIFA, nella seduta del 9, 10 e 11 aprile u.s., ha ritenuto di dare parere non favorevole ritenendo ancora troppo preliminari i dati scientifici a supporto dell'indicazione richiesta.

Cordiali saluti

Il Dirigente
Sandra Petraglia

Grazie dell'attenzione

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